

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

**NOTIFICATION OF ELECTION**  
(PCT Rule 61.2)

To:  
Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 10 July 2000 (10.07.00)
International application No. PCT/NL99/00673
International filing date (day/month/year) 02 November 1999 (02.11.99)

in its capacity as elected Office

Applicant's or agent's file reference  
BO 41745

Priority date (day/month/year)  
02 November 1998 (02.11.98)

**Applicant**

BESEMER, Arie, Cornelis et al

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

29 May 2000 (29.05.00)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer:  Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BO 41745	FOR FURTHER ACTION <span style="float: right;">See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)</span>	
International application No. PCT/NL99/00673	International filing date (day/month/year) 02/11/1999	Priority date (day/month/year) 02/11/1998
International Patent Classification (IPC) or national classification and IPC C08B37/00		
Applicant NEDERLANDSE ORGANISATIE VOOR TOEGEPAST...ET AL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I     Basis of the report
- II     Priority
- III     Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV     Lack of unity of invention
- V     Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI     Certain documents cited
- VII     Certain defects in the international application
- VIII     Certain observations on the international application

Date of submission of the demand 29/05/2000	Date of completion of this report 06.02.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Contet, F  Telephone No. +49 89 2399 8671



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL99/00673

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*):

Description, pages:

1-8 as originally filed

### Claims, No.:

1-9 as originally filed

10-14 as received on 05/12/2000 with letter of 05/12/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/NL99/00673

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims 6-11
	No:	Claims 1-5, 12-14
Inventive step (IS)	Yes:	Claims 8-11
	No:	Claims 6,7
Industrial applicability (IA)	Yes:	Claims 1-14
	No:	Claims

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL99/00673

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1 : US-A-2 894 945 &

D1a : 1 : AL. JEANES ET AL.: THE JOURNAL OF ORGANIC CHEMISTRY, vol. 20, no. 11, November 1955, pages 1565-1568 ( cited in D1, col.2, l.19-28)

D2 : B. ANN-CHRISTINE SALOMONSSON ET AL: 'Coupling of 1-aminododecan to starch by bromine oxidation and reductive amination' STARCH STARKE, vol. 44, no. 7, 1992, pages 260-263, XP002081699

**I- Novelty:**

The present application is concerned with a process for preparing an oxidised carbohydrate, wherein the moiety -CHOH-CHOH- of the carbohydrate is first oxidised in order to give a dialdehyde carbohydrate, which is then treated with molecular halogen, e.g. bromine, to oxidise a part of the aldehydes groups into carboxylic. The product thus obtained has a ratio aldehyde groups/carboxyl group of 25/75 to 80/20.

**1.1 :** The document D1 is concerned with the preparation of dialdehyde starch by first reacting starch with periodate and further oxidising the dialdehyde starch thus obtained with sodium chlorite in glacial acetic acid in order to achieve complete conversion of the carbonyl groups to carboxyl groups (col.1, line 21 - col.2, l. 18 and Examples I to IV).

The document D1a, cited in D1, discloses the preparation of dialdehyde starch by reacting starch with periodate. Said dialdehyde starch was further either reduced with Raney Nickel catalyst to obtain meso-erythritol (p.1566 and Summary) **or** oxidised with bromine in barium acetate buffered solution leading to a conversion of the aldehydes groups to carboxyl of max. 54% (D1a, p.1567 and see also D1, col.2, lines 19-28). In the second case the product P\* obtained shows both aldehyde and carboxylic groups.

Said product are further hydrolysed to D-erythronic lactone.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL99/00673

**1.2 : Claims 1 to 7 and 12 to 14:** Claim 1 intends to define the product in terms of a process of manufacture. Such a Claim is admissible only if the product as such fulfils the requirements for patentability, i.e. *inter alia* that it is new and inventive. A product is not rendered novel merely by the fact that it is produced by means of a new process (see the PCT/GL C III 4.7b.)

The product according to Claims 1 to 5 does not differ from the oxidised product P\* obtained according to D1a . Thus novelty of the claimed product cannot be acknowledged.

The products of Claims 12 to 14 are new over D1 and D1a.

**1.3 : Claims 8 to 11:** The process claimed differs therefrom by the use of bromine in catalytic amount in the second oxidation step and the subject-matter of present Claims 8 to 14 is new over this teaching.

**1.4 : Claims 12 to 14:** D2 discloses the aqueous bromine oxidation at pH 7 of starch and the introduction of both keto functions and carboxylic groups. The keto functions are further aminated by reductive amination with e.g. aminodecan (Abstract, points 1 to 2.2 and Table 1). According to page 263, left-hand column, last paragraph, amination of the keto groups introduced by oxidation is achieved at 80°C.

Therefore the claimed amino products, bearing both substituted amine groups and carboxy groups, do not differ from the products prepared according to D2 bearing the same groups.

**II- Inventive step :**

The document D1a is regarded as the closest prior art to the subject-matter of claim 1.

The fact to use modified starch cannot confer an inventive step either to the product obtained or to the process claimed.

The process according to present Claim 8 differs from the closest prior art D1a in that the oxidation system is bromine in a catalytic amount, obtained for example from the reaction product of a halide with a carboxylic peracid instead of bromine in barium acetate buffered solution.

The argument brought forward, that a lower extent of degradation is achieved and

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL99/00673

that a regular oxidation of the dialdehydes to mono-aldehyde-monocarboxylic functions occurs, has not been supported by evidence.

But it appears that the process claimed allows to modulate the conversion rate of the aldehyde function (see page 3, I.33-p.2, I.4). Further according to p.4, I.6-11, the product obtained shows structural regularity since the dialdehyde functions have been converted to mono-aldehyde-monocarboxylic functions.

This effect was not suggested from the available prior art and an inventive step can be acknowledged to the process claimed.

**III- Industrial applicability:**

Method for preparing oxidised polysaccharide.

**Re Item VII**

**Certain defects in the international application**

On page 3, lines 21 and in Ex. 1, page 5, I. 28,29, the definition of the oxidising agent should strictly follow the definition given in Claim 8 and 10.

The citation on page 1, last paragraph, reflecting the prior art D1a is not in accordance with the disclosure in said document D1a

**Re Item VIII**

**Certain observations on the international application**

- **Claims 1, 8 and 12 :** Claim 1 intends to define the product in terms of a process of manufacture. The applicant alleges that new and inventive products are obtained. Thus it appears that both products features and process features which are essential for the definition of the invention are missing. Thus Claim 8 is not drafted according to the point of view of patent law, in which a chemical production process is clearly defined by a statement of the initial substances, the process parameters and the end product and as to how it can be subsequently carried out.

BO 41745

12. 2000

PCT/NL99/00673

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10. A process according to claim 7 or 8, wherein the molecular halogen is produced in situ by reaction of halide with a carboxylic peracid.

11. A process for producing an oxidised, amino-substituted carbohydrate, comprising reductively aminating residual aldehyde groups in the oxidised carbohydrate obtained by the process according to any one of claims 8-10.

12. An amino-substituted oxidation product derived from a carbohydrate containing 1,2-dihydroxyethylene groups in its repeating units, these dihydroxyethylene groups having at least partially been oxidised to dialdehyde groups, the product containing on average 0.1-1.5 carboxyl groups and 0.1-1.9 substituted amine groups per oxidised 1,2-dihydroxyethylene group.

13. An amino-substituted oxidation product according to claim 12, containing on average 0.1-1.2 carboxyl groups and 0.3-1.2 substituted amino groups per repeating unit.

14. An amino-substituted oxidation product according to claim 12 or 13, wherein said substituted amino group has the formula  $-NR^1R^2$ , wherein  $R^1$  represents hydrogen, a C<sub>1</sub>-C<sub>20</sub> alkyl, alkenyl or alkynyl group optionally substituted with carboxy, hydroxy, C<sub>1</sub>-C<sub>12</sub> alkoxy, amino, carbamoyl and/or aryl, including natural and synthetic amino acid residues, and  $R^2$  represents hydrogen, amino, substituted amino, hydroxy, alkoxy, or a C<sub>1</sub>-C<sub>12</sub> alkyl, alkenyl or alkynyl group optionally substituted with carboxy, hydroxy, C<sub>1</sub>-C<sub>12</sub> alkoxy, amino and/or carbamoyl, or a substituted iminomethyl group, or  $R^1$  and  $R^2$ , together with the nitrogen atom to which they are bound, represent a three- to seven-membered heterocyclic system, optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted with carboxy, hydroxy, oxo, C<sub>1</sub>-C<sub>12</sub> alkyl, alkenyl, alkynyl or alkoxy, amino, carbamoyl and/or aryl

## PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BO 41745	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/NL99/00673	International filing date (day/month/year) 02/11/1999	Priority date (day/month/year) 02/11/1998
International Patent Classification (IPC) or national classification and IPC C08B37/00		
Applicant NEDERLANDSE ORGANISATIE VOOR TOEGEPAST...ET AL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

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- I    Basis of the report
- II    Priority
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- IV    Lack of unity of invention
- V    Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI    Certain documents cited
- VII    Certain defects in the international application
- VIII    Certain observations on the international application

Date of submission of the demand 29/05/2000	Date of completion of this report 06.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Contet, F  Telephone No. +49 89 2399 8671



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL99/00673

## I. Basis of the report

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**Description, pages:**

1-8                   as originally filed

### Claims, No.:

1-9                   as originally filed

10-14                as received on                   05/12/2000   with letter of                   05/12/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

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- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
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4. The amendments have resulted in the cancellation of:

- the description,           pages:
- the claims,               Nos.:
- the drawings,           sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/NL99/00673

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims 6-11
	No:	Claims 1-5, 12-14
Inventive step (IS)	Yes:	Claims 8-11
	No:	Claims 6,7
Industrial applicability (IA)	Yes:	Claims 1-14
	No:	Claims

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL99/00673

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1 : US-A-2 894 945 &

D1a : 1 : AL. JEANES ET AL.: THE JOURNAL OF ORGANIC CHEMISTRY, vol. 20, no. 11, November 1955, pages 1565-1568 ( cited in D1, col.2, I.19-28)

D2 : B. ANN-CHRISTINE SALOMONSSON ET AL: 'Coupling of 1-aminododecan to starch by bromine oxidation and reductive amination' STARCH STARKE, vol. 44, no. 7, 1992, pages 260-263, XP002081699

**I- Novelty:**

The present application is concerned with a process for preparing an oxidised carbohydrate, wherein the moiety -CHOH-CHOH- of the carbohydrate is first oxidised in order to give a dialdehyde carbohydrate, which is then treated with molecular halogen, e.g. bromine, to oxidise a part of the aldehydes groups into carboxylic. The product thus obtained has a ratio aldehyde groups/carboxyl group of 25/75 to 80/20.

**1.1 :** The document D1 is concerned with the preparation of dialdehyde starch by first reacting starch with periodate and further oxidising the dialdehyde starch thus obtained with sodium chlorite in glacial acetic acid in order to achieve complete conversion of the carbonyl groups to carboxyl groups (col.1, line 21 - col.2, I. 18 and Examples I to IV).

The document D1a, cited in D1, discloses the preparation of dialdehyde starch by reacting starch with periodate. Said dialdehyde starch was further either reduced with Raney Nickel catalyst to obtain meso-erythritol (p.1566 and Summary) **or** oxidised with bromine in barium acetate buffered solution leading to a conversion of the aldehydes groups to carboxyl of max. 54% (D1a, p.1567 and see also D1, col.2, lines 19-28). In the second case the product P\* obtained shows both aldehyde and carboxylic groups.

Said product are further hydrolysed to D-erythronic lactone.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL99/00673

**1.2 : Claims 1 to 7 and 12 to 14:** Claim 1 intends to define the product in terms of a process of manufacture. Such a Claim is admissible only if the product as such fulfils the requirements for patentability, i.e. *inter alia* that it is new and inventive. A product is not rendered novel merely by the fact that it is produced by means of a new process (see the PCT/GL C III 4.7b.)

The product according to Claims 1 to 5 does not differ from the oxidised product P\* obtained according to D1a . Thus novelty of the claimed product cannot be acknowledged.

The products of Claims 12 to 14 are new over D1 and D1a.

**1.3 : Claims 8 to 11:** The process claimed differs therefrom by the use of bromine in catalytic amount in the second oxidation step and the subject-matter of present Claims 8 to 14 is new over this teaching.

**1.4 : Claims 12 to 14:** D2 discloses the aqueous bromine oxidation at pH 7 of starch and the introduction of both keto functions and carboxylic groups. The keto functions are further aminated by reductive amination with e.g. aminodecan (Abstract, points 1 to 2.2 and Table 1). According to page 263, left-hand column, last paragraph, amination of the keto groups introduced by oxidation is achieved at 80°C.

Therefore the claimed amino products, bearing both substituted amine groups and carboxy groups, do not differ from the products prepared according to D2 bearing the same groups.

**II- Inventive step :**

The document D1a is regarded as the closest prior art to the subject-matter of claim 1.

The fact to use modified starch cannot confer an inventive step either to the product obtained or to the process claimed.

The process according to present Claim 8 differs from the closest prior art D1a in that the oxidation system is bromine in a catalytic amount, obtained for example from the reaction product of a halide with a carboxylic peracid instead of bromine in barium acetate buffered solution.

The argument brought forward, that a lower extent of degradation is achieved and

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL99/00673

that a regular oxidation of the dialdehydes to mono-aldehyde-monocarboxylic functions occurs, has not been supported by evidence.

But it appears that the process claimed allows to modulate the conversion rate of the aldehyde function (see page 3, I.33-p.2, I.4). Further according to p.4, I.6-11, the product obtained shows structural regularity since the dialdehyde functions have been converted to mono-aldehyde-monocarboxylic functions.

This effect was not suggested from the available prior art and an inventive step can be acknowledged to the process claimed.

**III- Industrial applicability:**

Method for preparing oxidised polysaccharide.

**Re Item VII**

**Certain defects in the international application**

On page 3, lines 21 and in Ex. 1, page 5, I. 28,29, the definition of the oxidising agent should strictly follow the definition given in Claim 8 and 10.

The citation on page 1, last paragraph, reflecting the prior art D1a is not in accordance with the disclosure in said document D1a

**Re Item VIII**

**Certain observations on the international application**

**- Claims 1, 8 and 12 :** Claim 1 intends to define the product in terms of a process of manufacture. The applicant alleges that new and inventive products are obtained. Thus it appears that both products features and process features which are essential for the definition of the invention are missing. Thus Claim 8 is not drafted according to the point of view of patent law, in which a chemical production process is clearly defined by a statement of the initial substances, the process parameters and the end product and as to how it can be subsequently carried out.

10. A process according to claim 7 or 8, wherein the molecular halogen is produced in situ by reaction of halide with a carboxylic peracid.
11. A process for producing an oxidised, amino-substituted carbohydrate, comprising reductively aminating residual aldehyde groups in the oxidised carbohydrate obtained by the process according to any one of claims 8-10.
12. An amino-substituted oxidation product derived from a carbohydrate containing 1,2-dihydroxyethylene groups in its repeating units, containing on average 0.1-1.5 carboxyl groups and 0.1-1.9 substituted amine groups per oxidised 1,2-dihydroxyethylene group.
13. An amino-substituted oxidation product according to claim 12, containing on average 0.1-1.2 carboxyl groups and 0.3-1.2 substituted amino groups per repeating unit.
14. An amino-substituted oxidation product according to claim 12 or 13, wherein said substituted amino group has the formula  $-NR^1R^2$ , wherein  $R^1$  represents hydrogen, a C<sub>1</sub>-C<sub>20</sub> alkyl, alkenyl or alkynyl group optionally substituted with carboxy, hydroxy, C<sub>1</sub>-C<sub>12</sub> alkoxy, amino, carbamoyl and/or aryl, including natural and synthetic amino acid residues, and  $R^2$  represents hydrogen, amino, substituted amino, hydroxy, alkoxy, or a C<sub>1</sub>-C<sub>12</sub> alkyl, alkenyl or alkynyl group optionally substituted with carboxy, hydroxy, C<sub>1</sub>-C<sub>12</sub> alkoxy, amino and/or carbamoyl, or a substituted iminomethyl group, or  $R^1$  and  $R^2$ , together with the nitrogen atom to which they are bound, represent a three- to seven-membered heterocyclic system, optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted with carboxy, hydroxy, oxo, C<sub>1</sub>-C<sub>12</sub> alkyl, alkenyl, alkynyl or alkoxy, amino, carbamoyl and/or aryl.

Nederlandsch Octrooibureau

## PATENT COOPERATION TREATY

INGEK. 19 MEI 2000

Paraaf Bewerken

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**NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES**

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year)

11 May 2000 (11.05.00)

Applicant's or agent's file reference

BO 41745

**IMPORTANT NOTICE**

International application No.

PCT/NL99/00673

International filing date (day/month/year)

02 November 1999 (02.11.99)

Priority date (day/month/year)

02 November 1998 (02.11.98)

Applicant

NEDERLANDSE ORGANISATIE VOOR TOEGEPAST- NATUURWETEN- SCHAPPELIJK  
ONDERZOEK TNO et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU,CN,JP,KP,KR,MA,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,  
GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,  
PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on  
11 May 2000 (11.05.00) under No. WO 00/26257

**REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)**

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

**REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))**

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

Authorized officer

J. Zahra

The International Bureau of WIPO  
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<p>(21) International Application Number: PCT/NL99/00673</p> <p>(22) International Filing Date: 2 November 1999 (02.11.99)</p> <p>(30) Priority Data: 98203706.1 2 November 1998 (02.11.98) EP</p> <p>(71) Applicant (for all designated States except US): NEDERLANDSE ORGANISATIE VOOR TOEGEPAST-NATUURWETEN - SCHAPPELIJK ONDERZOEK TNO [NL/NL]; Schoemakerstraat 97, NL-2628 VK Delft (NL).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): BESEMÉR, Arie, Cornelis [NL/NL]; H. van de Boschstraat 111, NL-3958 CC Amerongen (NL). JETTEN, Jan, Matthijs [NL/NL]; Costerlaan 3b, NL-3701 JL Zeist (NL). VAN DOREN, Hendrik, Arend [NL/NL]; Prins Bernhardlaan 5, NL-3818 ZE Amersfoort (NL). VAN DER LUGT, Jan, Pieter [NL/NL]; Schone van Boskoopgaarde 15, NL-3824 AA Amersfoort (NL).</p> <p>(74) Agent: DE BRUIJN, Leendert, C.; Nederlandsch Octrooibureau, Scheveningseweg 82, P.O. Box 29720, NL-2502 LS The Hague (NL).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p>	

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(54) Title: CARBOHYDRATE OXIDATION PRODUCTS AND DERIVATIVES

(57) Abstract

A novel oxidation product derived from a carbohydrate containing 1,2-dihydroxyethylene groups in its repeating units, can be obtained by at least partially oxidising the 1,2-dihydroxyethylene groups of the carbohydrate to dialdehyde groups, and oxidising a part of the aldehyde groups to carboxylic acid groups. The oxidation product has a regular structure with alternating aldehyde groups and carboxyl groups in a ratio of about 1:1. It can be further transformed to an amino-substituted oxidation product by reductive amination of a least a part of the remaining aldehyde groups.

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## CARBOHYDRATE OXIDATION PRODUCTS AND DERIVATIVES

The present invention relates to novel oxidation products of carbohydrates and derivatives  
5 thereof, and to processes of preparing these.

Several procedures are known in the art for subjecting chemical species containing 1,2-di-hydroxyethylene units to 'oxidative glycol cleavage', a carbon-carbon scission reaction which is accompanied by oxidation of the hydroxymethine groups to aldehydes or  
10 carboxylic acids. In polymeric carbohydrates, in which the 1,2-dihydroxyethylene units are usually part of a 5- or 6-membered ring, the carbon-carbon bond scissions do not lead to degradation of the polymeric chains. The best-known procedures for said conversions in carbohydrates are:

- sodium periodate oxidation to dialdehydes (see e.g. WO 95/12619), which, if so desired, can be followed by oxidation to the corresponding diacids by reaction with sodium chlorite and hydrogen peroxide, and
  - direct conversion of carbohydrates to diacids by reaction with sodium hypochlorite and a catalytic amount of bromine (see e.g. EP-A-427349).
- 20 In principle, such conversions can be carried out with any carbohydrate containing 1,2-di-hydroxyethylene units, but most of the work known in the art has been restricted to dialdehyde starch and dialdehyde inulin, and dicarboxylic starch and dicarboxylic inulin, respectively. Dialdehyde derivatives of carbohydrates have been reported to be useful as additives in papermaking processes (wet-end strengthening); dicarboxylic derivatives of  
25 carbohydrates are useful due to their capacity to bind divalent metal ions, notably calcium and magnesium ions.

Another reaction of dialdehyde starch was described by Jeanes and Hudson, *J. Org. Chem.* 20, 1565-1568 (1955). They heated the periodate-oxidised starch at 100°C for 45 minutes  
30 and then treated the cooled solution with barium acetate and 2 equivalents of bromine, ultimately resulting in the generation of erythritol and erythronic lactone from the periodate-oxidised starch. Under those heating conditions, the dialdehyde groups of the oxidised starch will disproportionate to carboxyl and alcohol groups by the well-known Cannizarro reaction. Moreover, the process is accompanied by considerable chain  
35 degradation. Thus the reaction product is not a polymeric product having appreciable levels of aldehyde groups in addition to the carboxylic groups.

It was found now that in 'dialdehyde carbohydrates', i.e. carbohydrates in which the 1,2-di-hydroxyethylene groups of the parent carbohydrate have been partly or completely converted to dialdehyde groups, one of the aldehyde groups can be selectively oxidised to a carboxyl group. The mono-carboxyl-monoaldehyde carbohydrate derivatives thus obtained have interesting properties and can be applied e.g. as temporary crosslinkers in polysaccharide solutions or suspensions or as reactive hydrophilic coatings. They are also versatile starting materials for further derivatisation, especially to amino derivatives, to obtain e.g. polymeric surfactants, emulsifiers or decoupling polymers. The carboxyl-aldehyde carbohydrates of the invention have an aldehyde to carboxyl ratio of between 25/75 and 80/20, especially between 40/60 and 75/25. They contain on average 0.1-1.5, preferably 0.5-1.3 carboxyl group, and 0.5-1.9, preferably 0.7-1.5 aldehyde group per oxidised 1,2-dihydroxyethylene group. Per total number of repeating units (including non-oxidised units if any), the products of the invention contain on average 0.1-1.2, preferably 0.2-1.0 carboxyl group and 0.2-1.5, preferably 0.3-1.2 aldehyde group per repeating unit.

The present invention also includes a new process for the oxidation of aldehyde groups to carboxylic groups in carbohydrate derivatives, in which only a catalytic amount of molecular halogen is required. The catalytic amount of halogen is regenerated in situ by oxidation with an oxidising agent. Preferably, this novel process comprises the use of peracids for the (re)generation of the molecular halogen instead of sodium hypochlorite. It was found that the novel process, besides reducing the amount of halide produced, is also beneficiary to the properties of the partially oxidised products, in that a lower extent of degradation is observed. In addition, this process is considerably cheaper than the oxidation with sodium chlorite in the presence of hydrogen peroxide.

The catalytic amount of molecular halogen may be 0.2-40, preferably from 1 to 10 mole%, with respect to the amount of peracid. The halogen may be chlorine, bromine or iodine. The peracid may be any peralkanoic acid such as peracetic acid, perpropionic acid, perlauric acid etc., a substituted peralkanoic acid such as peroxytrifluoroacetic acid, an optionally substituted aromatic peracid such as perbenzoic acid or m-chloroperbenzoic acid, or an inorganic peracid such as perboric or persulphuric acid.

The oxidised carbohydrate according to the invention can be derived from any carbohydrate containing 1,2-dihydroxyethylene groups in its recurring units, which carbohydrate contains a relatively low level of reducing end groups. Such carbohydrates include non-

reducing disaccharides and oligosaccharides, such as sucrose, raffinose, trehalose and similar oligosaccharides, and polysaccharides which are 1,2-, 1,4- or 1,6-linked. Examples include  $\alpha$ -1,4-glucans (the "starch family"),  $\beta$ -1,4-glucans (cellulose), glucomannans and galactomannans (guar and locust bean gum), (arabino)xylans (hemicellulose) and  $\beta$ -2,1- and  $\beta$ -2,6-fructans (inulin and levan). The starch-type carbohydrates, cellulose and inulin 5 are preferred carbohydrates.

Modifications of starch and other carbohydrates can also be used as starting materials, and comprise partially hydrolysed products, as well as physical and chemical modifications, 10 including hydroxyalkyl, carboxyalkyl and similar derivatives, as well as uronic analogues. Short-chain carbohydrate derivatives, including monosaccharides, in which the reducing end groups have been protected, e.g. as glycosides, are also suitable starting materials. The carbohydrates are oxidised to dialdehyde derivatives by (meta)periodate oxidation or any 15 other suitable method, such as methods using manganese oxides. The oxidation may be complete, i.e. the oxidised carbohydrate may exclusively consist of dialdehyde monose units, or the oxidation may be partial, i.e. to a degree of oxidation (dialdehyde monose units) of 0.1-0.99 or 0.2-0.8.

After (partial) oxidation of the 1,2-dihydroxyethylene groups in a carbohydrate to obtain 20 the corresponding dialdehyde derivative, this product is further oxidised by reacting it with molecular halogen, preferably bromine, in the presence of an oxidising agent such as hypochlorite or a suitable peracid, preferably peracetic acid. The reaction can be performed in an aqueous slurry or solution, at a pH of 3-7, preferably 4-6. The reaction temperature is typically from 0 up to 80°C, preferably up to 50°C, more preferably from 0°C to ambient 25 temperature. The reaction may be carried out in a closed system to avoid loss of halogen by evaporation. A product is obtained, in which 0.1-1.5, preferably 0.6-1.2, aldehyde function in each oxidised 1,2-dihydroxyethylene group has been converted to carboxylic acid groups. The carboxylic acid groups may be present in the product in the form of the free acids, their carboxylate salts (e.g. with metal or (substituted) ammonium ions), as 4-7 30 membered lactones, or as mixtures thereof. The remaining aldehyde groups may be present as such, in the form of their hydrates or as (hemi-)acetals or (hemi-)aldals.

Using the process of the invention, a distinct decrease in the reaction rate is observed when 35 the degree of oxidation reaches about 50%, i.e. when about 50% of the available aldehyde groups have been converted to carboxylic groups. It is believed that the oxidation takes place in such a manner that one of the aldehyde functions in each monomeric unit reacts

first, whereas the oxidation of the other aldehyde function proceeds more slowly, most likely due to the formation of stable cyclic hemi-acetals. As a result, the reaction can be stopped conveniently at this stage, and a product is obtained in which approximately equal amounts of aldehyde and carboxylic functions are present.

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The product has as a characteristic feature that essentially all dialdehyde functions have been converted to mono-aldehyde-monocarboxylic functions. In the case of amylose that has been converted fully to dialdehyde amylose, oxidation according to the process of the present invention will lead to a structurally regular product with alternating aldehyde and 10 carboxylic groups. So far, it has been notoriously difficult to obtain structural regularity in carbohydrates derivatives. The products of the invention provide novel material properties.

The oxidised carbohydrates of the present invention can also serve as starting materials for a range of derivatives. The aldehyde is especially useful as an anchor for further 15 derivatisation. The reaction of the residual aldehyde groups with amines is of particular interest and leads to products that are structurally quite different from reaction products of amines and dialdehyde functions. In the latter case, when primary amines are used, each amine group will usually react with both aldehyde groups in the dialdehyde moiety, supposedly leading to seven-membered rings incorporating one nitrogen atom (see Guthrie, 20 *Advances in Carbohydrate Chemistry*, Vol. 16, 1961). In the case of the oxidised carbohydrates of the present invention, however, the remaining aldehyde function of each mono-aldehyde-mono-carboxylic moiety will react with an amine group, leading to an acyclic moiety. The resulting products have interesting properties, associated with their zwitterionic (both cationic and anionic) nature and surface-active (both polar and apolar parts) and 25 metal-binding properties.

The amines that can be coupled to the mono-aldehyde-mono-acids include primary and secondary amines having the formula  $\text{HNR}^1\text{R}^2$ , with  $\text{R}^1$  and  $\text{R}^2$  as defined in the claims. Examples of amines are ammonia, alk(en)ylamines such as methyl, allyl, butyl, decyl, 30 hexadecyl or octadecenyl, dialkyl amines, cyclic amines such as pyrrolidines, piperidines, morpholines, thiazolines, imidazoles, tetrazoles, triazines etc., carboxy-substituted amines such as glycine, lysine or other  $\alpha$ -amino acids, or iminodiacetic acid, hydroxy-substituted amines such as diethanolamine, and diamines and polyamines such as hexamethylene-diamine, and further other amino-functional molecules that can react with aldehyde 35 functions such as hydrazine, hydrazides, hydrazone, hydroxylamines, amidines, guanidines, isothiourea's and the like. The latter can be used for crosslinking the carbohydrates.

Coupling of the amines to the aldehyde function results primarily in imines, which are usually not thermally and hydrolytically stable, and are, therefore, preferably reduced to the corresponding amines using conventional reducing agents such as borohydrides. The reductive amination can also be performed in a single step, using reducing agents such as 5 borohydrides or using pressurised hydrogen in the presence of a metal catalyst. These amination reactions as such are well-known to the skilled person.

The amino-substituted carbohydrate oxidation product of the invention may contain on average 0.1-1.5, preferably 0.3-1.3 carboxyl group and 0.1-1.9, preferably 0.3-1.5 10 substituted amine group per oxidised 1,2-dihydroxyethylene group. Per total number of repeating units (including non-oxidised units if any), they may contain on average 0.1-1.2, preferably 0.2-1.0 carboxyl group, and 0.1-1.5, preferably 0.3-1.2 substituted amino groups 15 per repeating unit. In addition to the amino groups, the product may or may not contain residual carbonyl (aldehyde) groups; in other words, the amination of the aldehyde groups may be partial or complete.

### Example 1

*Preparation of a starch derivative containing approximately equivalent amounts of aldehyde and carboxylic functions (Monoaldehyde monocarboxylic starch, MACS)*

20 *1a. Preparation of dialdehyde starch (DAS)*

122.5 grams (0.76 mole, based on anhydroglucose) of starch (weight corrected for dry matter content) are suspended in 500 ml of demineralised water. The suspension is brought to pH 4.5 and cooled to 5°C. Sodium periodate (165 g, 0.77 mole) is added and the suspension is stirred at 5°C in the dark for 20 hours. The dialdehyde starch obtained in this 25 fashion is isolated by filtration. The crude product is washed extensively with water until iodate can no longer be detected by reaction with potassium iodide.

*1b. Preparation of monoaldehyde monocarboxylic starch (MACS)*

The DAS thus prepared was oxidised further using bromine/peracetic acid. In order to oxidise approximately 50% of the aldehyde groups present, 0.76 mole of peracetic acid 30 (0.584 M solution, 1,3 l) was added in 14 portions to the well-stirred suspension of DAS in 1 l of water, to which 12 g (0.12 mole, corresponding to 0.06 mole of Br<sub>2</sub>) of sodium bromide had been added. This amount was sufficient to effect complete conversion of peracetic acid to acetic acid through oxidation of bromide to bromine, which is the oxidising species in the reaction. The pH was kept at 5 (addition of 0.1 N sodium 35 hydroxide solution, pH-stat) throughout the reaction and each consecutive portion of peracetic acid was added after the suspension/solution had turned colourless. Upon

completion of the reaction, the solution was desalinated by ultrafiltration, using a membrane with a cut-off MW 5000, and freeze-dried.

*Characterisation of MACS*

*Carboxylic acid content:* Desalinated MACS was dissolved in a small volume of demineralised water and eluted over a cation-exchange resin ( $H^+$ -form). The eluate was freeze-dried and titrated with sodium hydroxide solution. The carboxylic content was found to be about 0.7 carboxylic groups per monomer unit.

*Aldehyde content:* An excess of hydroxylammonium chloride was reacted with desalinated MACS. The hydrochloric acid that was liberated upon reaction with the aldehyde functions was titrated with sodium hydroxide solution. The aldehyde content was found to be about 1.2 aldehyde functions per monomer unit.

The ratio of aldehyde to carboxylic acid is therefore approximately 60-40.

**Example 2**

*Reductive amination of MACS with L-aspartic acid*

5.0 g of lyophilised MACS, prepared according to Example 1, are suspended in 150 ml of water whilst stirring. The suspension is stirred for another 30 minutes after which 7.5 g of aspartic acid are added. The pH is adjusted to 6.0 with 0.1 M hydrochloric acid solution and stirred for 48 hours, maintaining the pH at 6.0 using a pH-stat apparatus. During the 20 reaction 385 mg of sodium cyanoborohydride is added in portions of 30-40 mg, at regular intervals. After 48 hours, an additional 200 mg of sodium cyanoborohydride is added in one portion. Once the evolution of hydrogen has ceased, the pH is raised to 7.0 and any unreacted aspartic acid and inorganic salts are removed from the reaction mixture by means of nanofiltration and the residue is lyophilised.

25 The product was tested for its copper(II) binding capacity, using a copper(II)-selective electrode. 100 mg of product were dissolved in 100 ml of water and titrated with a 0.4 M  $CuCl_2$  solution until a residual  $Cu^{2+}$  concentration of  $1 \times 10^{-5}$  M had been reached. The copper-binding capacity was found to be 0.9 mmol/g.

**Example 3**

*Reductive amination of MACS with iminodiacetic acid*

1.0 g of lyophilised MACS, prepared according to Example 1, is suspended in 50 ml of water whilst stirring. The suspension is stirred for another 30 minutes after which 1.5 g (3 mmol) of iminodiacetic acid are added. The pH is adjusted to 6.0 with 0.1 M hydrochloric acid solution and stirred for 72 hours, maintaining the pH at 6.0 using a pH-stat

apparatus. During the reaction 378 mg of sodium cyanoborohydride is added in portions of 30-40 mg, at regular intervals. After 72 hours, an additional 200 mg of sodium cyanoborohydride is added in one portion. Once the evolution of hydrogen has ceased, the pH is raised to 7.0 and any unreacted iminodiacetic acid and inorganic salts are removed from the 5 reaction mixture by means of nanofiltration and the residue is lyophilised. It was determined by nitrogen analysis that only partial reductive amination (35-40 % of the available aldehyde groups) had taken place.

The product was tested for its copper(II) binding capacity, using a copper(II)-selective 10 electrode. 100 mg of product were dissolved in 100 ml of water and titrated with a 0.4 M CuCl<sub>2</sub> solution until a residual Cu<sup>2+</sup> concentration of  $1 \times 10^{-5}$  M had been reached. The copper-binding capacity was found to be 0,7 mmol/g.

#### **Example 4**

##### *Reductive amination of MACS with 1-octyl amine*

3.0 g of lyophilised MACS, prepared according to Example 1, are suspended in a well-stirred mixture of 200 ml of water and 50 ml of ethanol. The suspension is stirred for another 30 minutes after which 1.0 g of sodium cyanoborohydride is added. The pH is adjusted to 6.0 with 0.1 M hydrochloric acid solution and 548 mg (25 mol-% with respect 20 to the aldehyde groups MACS) of 1-octyl amine are added dropwise whilst maintaining the pH at 6.0 using a pH-stat apparatus. Stirring and pH-control are continued overnight. The pH is raised to 7.0 and any unreacted 1-octyl amine and inorganic salts are removed from the reaction mixture by means of nanofiltration and the residue is lyophilised.

The surface tension reduction of the product was measured as a function of its 25 concentration, using a drop tensiometer. The results are shown in Table 1.

#### **Example 5**

##### *Reductive amination of MACS with 1-dodecyl amine*

3.0 g of lyophilised MACS, prepared according to Example 1, are suspended in a well-stirred mixture of 200 ml of water and 50 ml of ethanol. The suspension is stirred for another 30 minutes after which 1.0 g of sodium cyanoborohydride is added. The pH is adjusted to 6.0 with 0.1 M hydrochloric acid solution and 785 mg (25 mol-% with respect 30 to the aldehyde groups present in MACS) of 1-dodecyl amine are added dropwise whilst maintaining the pH at 6.0 using a pH-stat apparatus. Stirring and pH-control are continued overnight. The pH is raised to 7.0 and any unreacted amine and inorganic salts are removed 35 from the reaction mixture by means of nanofiltration and the residue is lyophilised.

The surface tension reduction of the product was measured as a function of its concentration in water, using a drop tensiometer. The results are shown in Table 1.

5 *Table 1. Surface tensions of aqueous solutions of the products prepared according to Examples 4 and 5, as determined with a drop tensiometer.*

Concentration (g/l)	Surface tension (mN/m) at 25 °C	
	Example 4 (N-octyl)	Example 5 (N-dodecyl)
0.1	70.7	68.9
0.5	61.2	57.7
1.0	52.3	52.2
2.0	48.0	47.4
5.0	43.8	38.6
10	41.9	29.4
25	40.4	30.7

A significant lowering of the surface tension was observed, the largest effect being  
10 observed for the dodecyl amino derivative, which is in agreement with theoretical predictions.

**Claims**

1. An oxidised carbohydrate derived from a carbohydrate containing 1,2-dihydroxyethylene groups in its repeating units, the 1,2-dihydroxyethylene groups having at least partially been oxidised to dialdehyde groups, and a part of the aldehyde groups having been oxidised to carboxylic acid groups, the ratio between aldehyde groups and carboxyl groups being between 25/75 and 80/20.
2. An oxidised carbohydrate according to claim 1, containing on average 0.1-1.5 carboxyl groups and 0.5-1.9 aldehyde groups per oxidised 1,2-dihydroxyethylene group.
3. An oxidised carbohydrate according to claim 2, containing on average 0.5-1.3 carboxyl groups and 0.7-1.5 aldehyde groups per oxidised 1,2-dihydroxyethylene group.
4. An oxidised carbohydrate according to any one of claims 1-3, containing on average 0.1-1.2 carboxyl groups and 0.3-1.2 aldehyde groups per repeating unit.
5. An oxidised carbohydrate according to claim 1 or 2, wherein the carbohydrate is starch, amylose or amylopectin or a modification thereof.
6. An oxidised carbohydrate according to claim 1 or 2, wherein the carbohydrate is cellulose or a modification thereof.
7. An oxidised carbohydrate according to claim 1 or 2, wherein the carbohydrate is a 2,1-fructan.
8. A process for producing an oxidised carbohydrate according to any one of claims 1-7, comprising oxidising a dialdehyde carbohydrate obtainable by oxidising a carbohydrate containing 1,2-dihydroxyethylene groups in its repeating units, the oxidation of the dialdehyde carbohydrate being performed with a catalytic amount of molecular halogen, in particular molecular bromine.
9. A process according to claim 8, wherein the oxidation with molecular halogen is performed at a pH between 3 and 7.

10. A process according to claim 7 or 8, wherein the molecular halogen is produced in situ by reaction of halide with a carboxylic peracid.

11. A process for producing an oxidised, amino-substituted carbohydrate, comprising reductively aminating residual aldehyde groups in the oxidised carbohydrate obtained by the process according to any one of claims 8-10.

12. An amino-substituted oxidation product derived from a carbohydrate containing 1,2-dihydroxyethylene groups in its repeating units, containing on average 0.1-1.5 carboxyl groups and 0.1-1.9 substituted amine groups per oxidised 1,2-dihydroxyethylene group.

13. An amino-substituted oxidation product according to claim 12, containing on average 0.1-1.2 carboxyl groups and 0.3-1.2 substituted amino groups per repeating unit.

14. An amino-substituted oxidation product according to claim 12 or 13, wherein said substituted amino group has the formula -NR<sup>1</sup>R<sup>2</sup>, wherein R<sup>1</sup> represents hydrogen, a C<sub>1</sub>-C<sub>20</sub> alkyl, alkenyl or alkynyl group optionally substituted with carboxy, hydroxy, C<sub>1</sub>-C<sub>12</sub> alkoxy, amino, carbamoyl and/or aryl, including natural and synthetic amino acid residues, and R<sup>2</sup> represents hydrogen, amino, substituted amino, hydroxy, alkoxy, or a C<sub>1</sub>-C<sub>12</sub> alkyl, alkenyl or alkynyl group optionally substituted with carboxy, hydroxy, C<sub>1</sub>-C<sub>12</sub> alkoxy, amino and/or carbamoyl, or a substituted iminomethyl group, or R<sup>1</sup> and R<sup>2</sup>, together with the nitrogen atom to which they are bound, represent a three- to seven-membered heterocyclic system, optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted with carboxy, hydroxy, oxo, C<sub>1</sub>-C<sub>12</sub> alkyl, alkenyl, alkynyl or alkoxy, amino, carbamoyl and/or aryl.

# **INTERNATIONAL SEARCH REPORT**

**Item** **and Application No.**

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A. CLASSIFICATION OF SUBJECT MATTER		IPC 7 C08B37/00		C08B31/18		C08B15/02		C08B15/06		C08B37/18	
According to International Patent Classification (IPC) or to both national classification and IPC											
<b>B. FIELDS SEARCHED</b>											
Minimum documentation searched (classification system followed by classification symbols)											
IPC 7 C08B											
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched											
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)											
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>											
Category *	Citation of document, with indication, where appropriate, of the relevant passages									Relevant to claim No.	
X	US 2 894 945 A (B. T. HOFREITER) 14 July 1959 (1959-07-14) column 2, line 19 - line 28 & AL. JEANES ET AL.: THE JOURNAL OF ORGANIC CHEMISTRY, vol. 20, no. 11, November 1955 (1955-11), pages 1565-1568, usa page 1566, line 26 - line 41 page 1567, line 4 - line 16  -/-/									1-5, 8	
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.											
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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